EPIDEMIOLOGICAL ASPECTS OF AN OUTBREAK OF ENCEPHALOMYELITIS AT THE ROYAL FREE HOSPITAL, LONDON, IN THE SUMMER OF 1955

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(With 5 Figures in the Text)

INTRODUCTION

In the latter half of 1955, The Royal Free Hospital Teaching Group, with a total staff of about 3500, experienced an epidemic of an obscure illness which affected more than 300 people. More than half the cases occurred in July and August. Between 13 July and 24 November, 255 people were admitted to the Royal Free Hospital, while the remainder were either nursed at home or admitted elsewhere.

CLINICAL FEATURES

At onset the disease was marked by complaints of sore throat, and by headache, stiff neck, dizziness, blurred vision and bodily prostration. While there was usually a low-grade fever, the pharynx was rarely much inflamed, though the posterior cervical glands were tender and enlarged. Within a week of onset, more often after 3 or 4 days, there was a further reaction marked by vertigo, diplopia, paraesthesiae, pareses, asthenia, myalgia, apathy and depression. More than half the cases then showed varying degrees of lympho-reticular disturbance. Glands, liver and sometimes spleen, though rarely enlarged, became very tender, and morphological abnormalities were seen in the circulating lymphocytes. In the more severe forms of the disease both irritative and paralytic phenomena of variable distribution and duration appeared during the second and third weeks, and were not uncommonly accompanied by phases of psychological disturbance. The milder cases recovered without undergoing serious motor dysfunction, and were discharged within a month. Cases graded as moderate were warded for 1–3 months, and severe cases remained in hospital for 4 months or longer. The clinical features of the frank syndrome are described in detail elsewhere (Richardson, 1956; Compston, 1956; Dimsdale, 1957*a*, *b*). There were no fatal cases.

Host reactions

The cases fell into three groups, which it would be misleading to distinguish by too sharp a definition. Between 60 and 70% of cases had some degree of objective neurological involvement, varying from extremely mild to very severe. Many hosts reacted to infection by a display of irritability in the reticulo-endothelial system, varying from localized glandular enlargements to systemic reaction involving liver and spleen; certain cases of this type simulated infectious mononucleosis.

The neurological involvement was not necessarily correlated with the intensity of lympho-reticular reaction, and many of the most severe neurological cases showed minimal lympho-reticular reaction, but about a third, all graded severe and moderately severe, showed both types of host reaction. The clinical severity of 263 cases is shown in Table 1. Three main clinical types of neurological disorder were distinguished (Dimsdale, personal communication), namely cerebral, brain-stem and spinal. The last simulated acute anterior poliomyelitis and the first was compatible with several of the viral encephalitides, of which the presenting features are shown in Table 9.

Table 1. *Variations in host reaction and clinical severity of* 263 *cases*

No. of cases with lympho-reticular involvement	No. of cases with objective neurological disorder			No. of cases without objective neurological disorder all mild (includes abortive)
	Severe	Moderate	Mild	
None or minimal lymphadenopathy	14	33	40	44
Moderate to severe systemic reaction	6	39	29	68
Total	20	72	69	112
Qualitative changes in mononuclear series of white cells				
Positive	16	33	42	49
Negative	4	39	27	63
Total	20	72	69	112

The incubation period

Few instances of single isolated exposure were found among the cases which occurred in hospital staff, but there were several cases among relatives and friends of staff who had paid single visits to one of the hospitals. There were also several instances of either husbands or wives of staff who contracted the disease in their homes. The sum of their evidence suggests that the incubation period was 7 days or less, and 5–6 days for the majority. The best examples available are shown in Table 2. The short time-span of the many successive minor epidemics which made up the whole lends support to this estimate.

Abortive and silent infections

Abortive infections. During the course of the epidemic about 500 people complained of some of the prodromal symptoms. More than 400 of these reported sick, and of those examined soon after onset 326 developed the frank syndrome. Among the rest not all were seriously indisposed for more than one or two days; some did not seek medical advice until characterizing features of the disease had passed off. At present, while the aetiology of the disease remains unknown, it is uncertain how many of the suspects experienced an abortive infection, and how many may be regarded as subclinical and threshold infections. At a rough estimate the ratio of clinical cases to suspects was 3:1 in the beginning, and 3:2 after the peak period of

the week ending 23 July. The Hospital population was by then 'epidemic conscious', and more people reported sick with ill-defined malaise which at other times would have been called 'a touch of 'flu'.

Silent infections. Certain cases which occurred in private households are shown in Table 3. In three cases doctors working in the Teaching Group were the only link between the patient and the Royal Free Hospital.

Table 2. *Instances of case to case infection: the incubation period*

Case	Date of onset, first host	Contact case	Date of exposure to first host	Date of onset second host	Apparent incubation period
Case no. 43, nursing sister*	23. vii. 55	Case no. 143, research worker	20. vii. 55	27. vii. 55	7 days
Case no. 198, student nurse*	14. vii. 55	Fiancé	16. vii. 55	22. vii. 55	6 days
Case no. 144, in-patient*	2. viii. 55	Case no. 189, husband	29. vii. 55	3. viii. 55	5 days
Case no. 20, house officer†	28. xii. 55	Fiancé	Before 28. xii. 55	1. i. 56	Not less than 4 days
Case no. 131, medical student	23. vii. 55	Case no. 132, husband	Before 23. vii. 55	27. vii. 55	Not less than 4 days
Case no. 217, registrars' clerk	9. viii. 55	Sister	Before 9. viii. 55	15. viii. 55	Not less than 6 days
Case no. 257 finance clerk	17. viii. 55	Case no. 285, husband	Before 17. viii. 55	21. viii. 55	Not less than 4 days

* Single isolated exposure.
† Infective during relapse or re-infection.

Table 3. *Instances of persons apparently infected by symptomless carriers*

Clinical case	Date of exposure	Date of onset	Contact: ?silent case	Incubation period
Housewife	9 to 18. vii. 55	18. vii. 55	Husband (physician at Royal Free Hospital)	Not longer than 9 days
Housewife	21 to 28. viii. 55	28. viii. 55	Husband (physician at Royal Free Hospital)	7 days
House officer (elsewhere)	5. viii. 55	12. viii. 55	House officer at Royal Free Hospital	7 days
House officer (elsewhere)	1. viii. 55	6. viii. 55	House officer at Royal Free Hospital	6 days
Laboratory technician (elsewhere)	29. xi. 55	6. xii. 55	Visited Royal Free Hospital staff club	7 days

Course of the outbreak

The course of the outbreak is shown in Figs. 1 and 2. The first cases occurred at the Royal Free Hospital in Gray's Inn Road, W.C. 1 (see Fig. 2) with the largest community in the Teaching Group (Table 4). On 13 July a nursing sister and a casualty officer were admitted to the private block at the Liverpool Road Annexe with a tentative diagnosis of glandular fever. By date of onset the first case was

that of the nursing sister, who was working in the Ear-Nose-Throat-Eye block at Gray's Inn Road. She complained of diarrhoea on 18 June, followed by a severe attack of facial herpes at its worst about 22 June. While warded in the Sick Bay for the next 9 days she was frequently visited by another sister, who had prodromal symptoms on 6 July and became the third case. During the following month 14 out

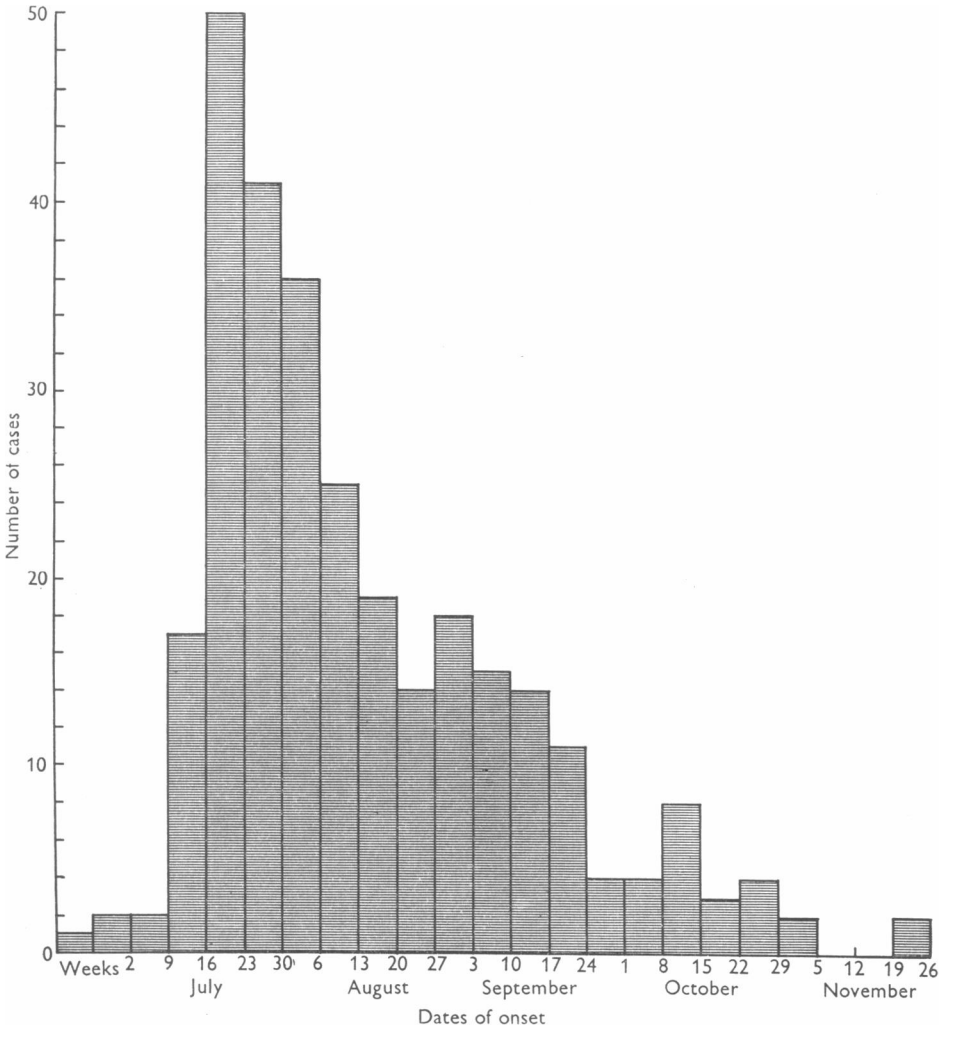

Fig. 1. Cases of epidemic disease by dates of onset: R.F.H. group.

of 25 nurses working in one part or another of the Ear-Nose-Throat-Eye section were admitted to hospital. The Casualty Out-patient Department experienced the second minor epidemic; 9 people contracted the disease in the following month. The chronological record of the first 50 cases by date of onset shows that by 13 July, the day of the first admissions, there were already some 30 people working at Gray's Inn Road who were in the incubation period. These included not only nurses, but

also medical, domestic and administrative staff, of whom several moved freely between hospitals in the Group.

In the week ending 16 July there were 17 cases at Gray's Inn Road. In the following week 50 cases were admitted, including 2 from the Liverpool Road Annexe. Further outbreaks at 7- to 10-day intervals occurred in succession among other communities in the Teaching Group (Fig. 2).

COMMUNICABILITY

Period of infectivity. The majority of cases were admitted after the theoretical period of maximum infectivity; only about a third were admitted within 2 days of onset. The time-lag between the date of onset and date of admission shortened as the outbreak progressed. Thus, in the beginning the infected hosts remained ambulant in the largest community of the Teaching Group at Gray's Inn Road, providing opportunity for dissemination of the infectious agent—whatever this may have been—throughout the entire period of infectivity. The explosive character and size of the outbreak at Gray's Inn Road created an impression of high infectivity, which was further supported by the rapid spread of the outbreak to the other hospitals in the Group. After the peak period, old and new cases were nursed at the Liverpool Road Annexe which became the isolation hospital and where the case incidence among the staff was higher than elsewhere in the Teaching Group (25 %). This hospital however received the high proportion of theoretically infectious cases which were among the later admissions. Cases among the medical officers who were attending new admissions contributed to the high incidence at Liverpool Road.

In two instances, individual hosts were apparently highly infectious for their contacts, before, during and after the onset of the disease. Neither case was severe, nor was infectivity correlated with the neuropathic form of the disease; both were marked by relative severity of the lymphoreticular response. The cases attributed to contact with either individual included several of the clinical types described on p. 103.

Return cases. No return cases can be cited as true instances of secondary attack. Relapses, recrudescences and possible re-infections during convalescence were a feature of the epidemic disease. It seemed remarkable that, if the aetiological agent was highly infectious *per se*, the disease did not, as far as it is known, spread to any great extent in the homes of non-resident staff. It was possible that hosts were either infectious for only a few hours, or that individual hosts varied widely in their infectivity for contacts, or that the hospital environment contained factors contributing to the communicability of the disease which were either submerged or lacking in the home.

Susceptibility of the hospital community

Table 4 shows the number of cases which occurred in different establishments and the dates of onset of the first and last cases at each place. The explosive character of the successive epidemics is best illustrated by the outbreaks at the

Preliminary Training School (10 days) and the Hampstead General Hospital (12 days) shown in Fig. 2.

Topography and population. The Teaching Group comprises the Royal Free Hospital, its two branches, and its associated hospitals, the Elizabeth Garrett

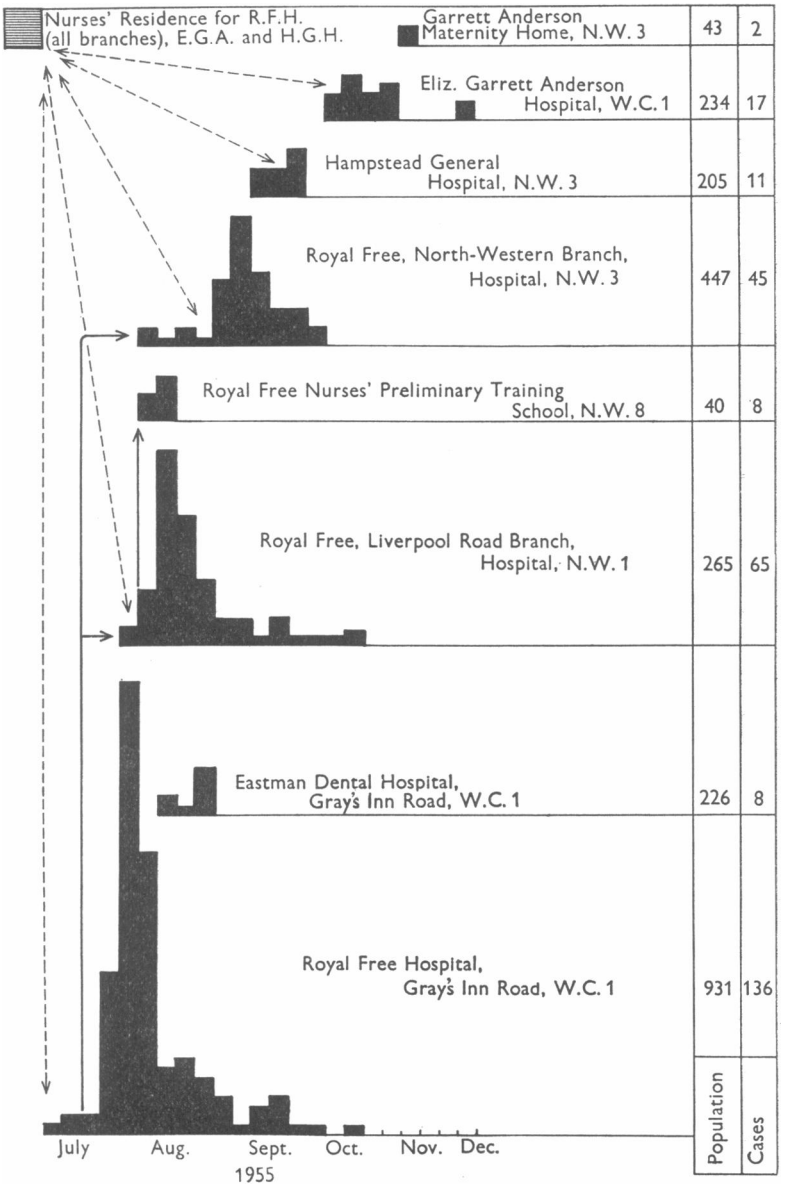

Fig. 2. Cases of epidemic disease by hospital (dates of onset).

Anderson and the Hampstead General. The Eastman Dental Hospital which adjoins the Royal Free Hospital in Gray's Inn Road also receives students of the Royal Free Hospital School of Medicine. There are, in addition, two preliminary training schools for nurses, and three extra residences for nursing and domestic

Table 4. *The successive epidemics in the Royal Free Hospital Teaching Group*, 1955

	Address	Beds	Population*	No. of cases	%	Time span of epidemic by date of onset: First case	Last case
The Royal Free Hospital	Gray's Inn Rd., W.C. 1	224	931	136	15	18. vi. 55	13. x. 55
Royal Free Hospital Annexe	Liverpool Rd., N. 1	142	265	65	25	19. vii. 55	12. x. 55
Royal Free Nurses' P.T.S.	College Cres., N.W. 8	—	40	8	20	26. vii. 55	8. viii. 55
Royal Free Hospital (North-Western branch)	Lawn Rd., N.W. 3	279	447	45	10	30. vii. 55	30. ix. 55
Eastman Dental Hospital	Gray's Inn Rd., W.C. 1	†	226	8	4	2. viii. 55	24. viii. 55
Hampstead General Hospital	Haverstock Hill, N.W. 3	140	205	11	5	8. ix. 55	22. ix. 55
Garrett Anderson Hospital	Euston Rd., W.C. 1	165	234	17	7	4. x. 55	24. xi. 55
Garrett Anderson Maternity Home	Belsize Grove, N.W 3	†	43	2	5	29. x. 55	5. xi. 55

* Staff only. Medical students and patients are included in the total population of about 3500.

† Beds included in Royal Free or Garrett Anderson.

staff. The Hampstead General Hospital maintains an out-patients' department on an entirely separate site, and the Elizabeth Garrett Anderson Hospital maintains a separate maternity home and convalescent home. A map of the district (Fig. 3) shows the sites of the different hospitals, and the main lines of intercommunication in the Teaching Group are shown in Fig. 4.

In nearly every occupational group certain members of the staff were shared by two or more hospitals, providing opportunities for cross-infection by host to host spread, which were limited but not eliminated by a standstill injunction on 24 July, closing the main Hospital at Gray's Inn Road and forbidding ancillary medical staff to carry out duties in more than one hospital. In Gray's Inn Road and at Hampstead, however, staff of adjoining hospitals patronize the same tobacconist and, of necessity, stand together at the same bus stops.

Attack rate in the hospital population

The case incidence, by sex, age and domicile, is shown in Tables 5 and 6. There were more than twice as many women as men in the population, and only over the age of 40 were men and women at risk in about equal numbers. With the exception of medical staff, the majority of the men were engaged in portering, maintenance, storekeeping, catering and administration. The women, on the other hand, were engaged not only in nursing (the largest occupational group) but were employed in all those branches of the auxiliary medical services which have personal contact with both nurses and patients, e.g. physiotherapy, radiography. The paediatric wards at Liverpool Road Annexe were closed at the beginning of the epidemic, and

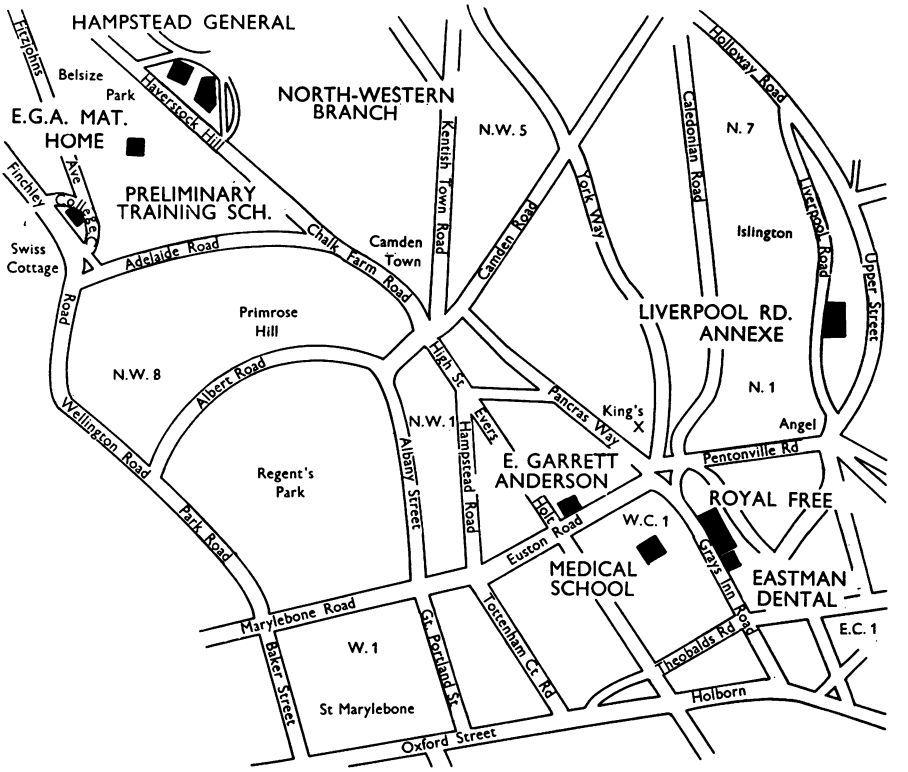

Fig. 3. The Royal Free Hospital Teaching group.

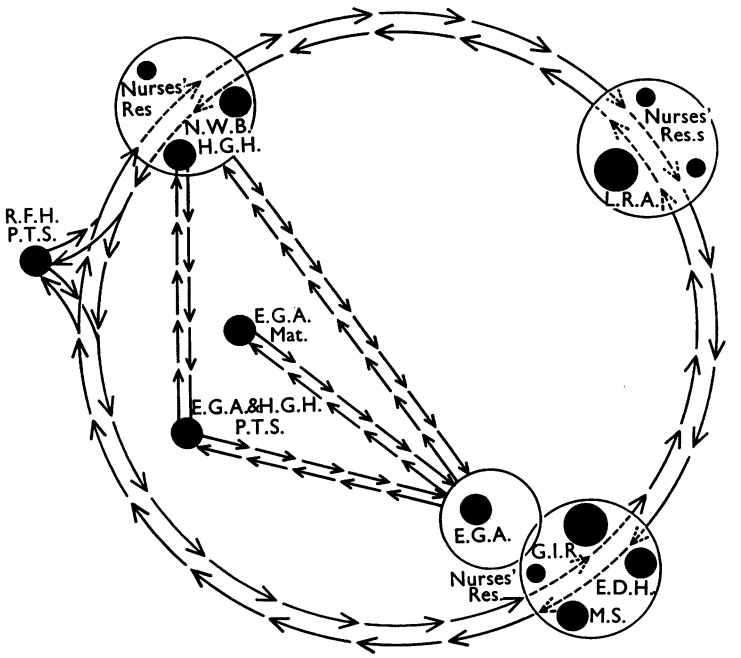

Fig. 4. Group intercommunications. G.I.R. = Royal Free Hospital, Gray's Inn Road; L.R.A., N.W.B. = branches of the Royal Free Hospital; E.G.A. = Elizabeth Garrett Anderson Hospital; H.G.H. = Hampstead General Hospital; P.T.S. = Preliminary Training School; E.D.H. = Eastman Dental Hospital; M.S. = Medical School.

Table 5. *Attack rate among men and women living in and out*

Sex	Population at risk	No. of cases	Attack rate per 100 in same category
Both sexes	3500	292	8·3
Non-resident	2740	128	4·7
Resident	860	164	19·0
Male	950	27	2·8
Non-resident	930	23	2·5
Resident	20	4	20·0
Female	2550	265	10·4
Non-resident	1710	105	6·1
Resident	840	160	19·0

Table 6. *Incidence of cases in different age groups among nurses*

Nurses	Nos. in different age groups: Under 20	20–30	30–40	Over 40	Totals
Nos. at risk in age group	200	450	120	30	800
Nos. of cases in age group	41	84	14	10	149
Percentage among members of one age group	20·5	18·6	11·6	33·3	—

thereafter no children were at risk as in-patients. The population of the Royal Free Group was therefore unrepresentative of the population as a whole.

The case incidence, whether related to the female population or to the total population, was highest among nurses. Amongst senior nurses it was disproportionately high, even allowing that the estimate of 33·3 % is inflated by paucity of numbers. It seems probable that certain senior nurses were, like certain medical officers, subjected to an exceptional degree of exposure by reason of their status. It also seems clear from the figures in Table 5 that residents were at least three times more liable to attack than the non-residents. The majority of resident nurses were either under 30 or over 40. Non-resident nurses were in the 30–40 age group.

Degree of exposure

Since the disease had probably originated, and had certainly spread, among the nursing staff, an attempt was made to measure the exposure of nurses both one to another and to other members of the staff. Nursing duties are too varied from day to day and from ward to ward to estimate the number of times one nurse may be within droplet distance of another nurse; it is certain, however, that a nurse is either (1) on duty, (2) at meals, (3) in transit, (4) off duty, in or out of hospital, or (5) asleep.

Other members of staff were grouped by work in relation to contact with nurses, and by communal dining rooms in relation to each other. Non-resident caterers and cooks, for example, had no personal contact with nurses, but were exposed to infection through contact with resident catering staff who were living in the nurses'

home. The 'exposure groups' are shown in Table 7, based on a points system of one point for residence, one for work-contact, etc. By this scheme nurses had four points, but no other occupational group had more than two points. The position of hospitalized patients was equivocal. Some patients required frequent lifting and personal service, e.g. those in Rheumatology wards. Others required little attention and spent much of their time in the open air. For this purpose medical officers and in-patients were regarded as being at equal risk (two points). The findings pointed to degree of exposure as the major factor determining the high case incidence in nurses of all age groups (see Table 8). Orderlies and domestic workers giving personal service to nurses (e.g. dining-room maids) were next in order of group susceptibility.

Table 7. *Degree of exposure of nurses to contact with other nurses in comparison with other members of the staff*

(Groups A, C, D, E, F and G each share a separate communal dining room. + +, repeated daily contact; +, possibility of daily contact; −, chance contact.)

	Nurses' contacts					
	On duty in hospital	At meals in nurses' home	In transit between ward/department and nurses' home	Off duty in nurses' home	Off duty, out	Opportunities for personal contact
A. Nurses	+ +	+ +	+ +	+ +	+	4
B. In-patients	+ +	−	−	−	−	1
C. Orderlies	+ +	−	+	−	−	2
Resident maids	−	+ +	−	+ +	−	2
D. Medical officers	+ +	−	−	−	−	1
E. Medical students	+	−	−	−	−	1
Radiographers, physiotherapists, almoners	+	−	−	−	−	1
Technicians, maintenance staff	+	−	−	−	−	1
Clerks and misc.	−	−	−	−	−	−
F. Porters, drivers	−	−	−	−	−	−
G. Catering and cooking staff	−	−	−	−	−	−

Table 8. *Attack rate in relation to degree of exposure to infection*

Degree of exposure	Classification	Population at risk	No. of cases	Attack rate per 100 at risk (%)
1st	Nurses	800	149	18·6
2nd	Resident domestics	240	33	13·7
3rd	Doctors and in-patients	200	28	14·0
4th	Ancillary medical, technical and social workers	200	26	13·0
5th	Others	2060	46	2·2

MODE OF SPREAD

The weather. The beginning of the epidemic coincided with the longest spell of hot dry weather experienced in the United Kingdom since the summer of 1947. During this period the mean temperature was consistently higher than average in the low-lying west central district of London (measured at Camden Square). This area, which is the scene of large demolitions and rebuilding, is always dustiest in the summer time and became noticeably more so during the hot dry spell.

Investigation of common vehicles

The explosive character of the outbreak at Gray's Inn Road suggested that the infectious agent might be spread by a common vehicle.

Water, milk and food. There was no evidence that either water or milk supplies were a source of infection, nor had any of the non-resident catering staff suffered from an illness resembling glandular fever, although 6 cooks became cases in the middle and at the end of the epidemic at Gray's Inn Road. A resident kitchen maid had been ill in May 1955 (the doubtful case of German measles mentioned on p. 117). By date of onset the fifth epidemic case was that of a resident maid working in the dining rooms used by the orderlies and resident domestic staff including kitchen maids. Two resident maids using the same dining room were among the next 10 cases: a diet-kitchen maid and the Matron's maid. The possibility of a subclinical case or symptomless carrier among the resident domestic staff cannot be ruled out, but there was nothing to connect the first dining-room maid with the first batch of nurses.

Laundry. Three laundresses working at the North-Western branch of the Royal Free Hospital were admitted to hospital, two having the epidemic disease and the third with a diagnosis of infective laryngitis. At the time of the first of these cases the epidemic had already broken out at the Liverpool Road Annexe and the North-Western laundry was taking in work from both Liverpool Road and from the Hampstead General Hospitals. There were no cases among laundry workers at Gray's Inn Road. While it seems possible that dirty linen may have been a source of infection to the laundry workers, they contracted the disease after cases were already occurring among other ancillary medical staff, and they were therefore exposed to infection from another source.

Possible vectors. There was no evidence of any sudden increase or change in the constitution of the usual insect population except a plague of clothes-moths. There was also no instance of epizootic disease among either experimental or domestic animals which might have affected the human population.

Possible chemical agents. It seemed possible that the disease could have been caused by the accidental introduction of a neurotoxic substance such as an insecticide, but no new insecticides had been introduced within recent months by the official controllers, and there was no report of any unofficial fly-spraying on a large scale. The possibility that trace-chemicals were introduced during renovations was also considered. The same proprietary brands of paint, distemper and detergent had been in general use for 10 years. None of the newest emulsion paints, alleged

to contain cadmium, had been used in any of the communal rooms. Had any unusual chemical aerosol been accidentally created at Gray's Inn Road, it seems probable that factory hands on an adjoining site would have been affected too, for owing to the hot weather, windows in the hospital and neighbourhood were wide open night and day.

Washing-up materials. The detergent used by the catering staff and canteen workers, and widely used in the Hospital, had been repeatedly tested for bactericidal activity in the Department of Bacteriology. Re-tested in comparison with the detergent powder used in the Nurses' Home for washing up, there was no evidence that the bactericidal activity of either substance was inadequate for its purpose. The detergent powder was submitted for a chemical analysis and no harmful ingredients or trace-substances were found.

Chronological order of the cases

At Gray's Inn Road the order of the first 10 epidemic cases was thus—1, 2, 3: nursing staff; 4: medical officer; 5: dining-room maid; 6: Nurses' Home lodge-keeper; 7: medico-social worker; 8, 9, 10: nursing staff. At the North-Western branch the order was different, namely—1: medico-social worker; 2: registrars' clerk; 3: pastry cook; 4: laundress; 5: medical student; 6: hospitalized patient; 7–10: nursing staff. In the latter group, cases 1, 3 and 5 were contacts of people working at Gray's Inn Road who became cases of suspects shortly after the date of contact (4–8 days). At the Liverpool Road Branch the first cases were among nurses, doctors and patients, while at the Elizabeth Garrett Anderson the first case was the Matron.

Host to host spread

The primary reaction in the throat and posterior cervical glands suggested the nasopharynx as one probable portal of entry for the infectious agent. In 11 cases herpetic vesicles were seen in either mouth or throat at the time of admission. Several patients complained of 'prickly sensations at the back of the throat' and of 'gravel' or 'crumbs' in the post-nasal region. Three patients with latent herpes simplex had skin eruptions of varying severity before onset of prodromal symptoms, in two cases the herpes having appeared about a week before onset. It was possible that damaged skin or mucous membrane also occasionally provided a portal of entry. A few patients had diarrhoea at onset, mentioned as an incidental complaint rather than a presenting symptom. The evidence regarding the mode of entry also suggested droplet infection as one possible mode of exit, though in many viral infections the infectious agent is liberated in faeces.

From the beginning instances of presumable case-to-case infection were recorded, and probable cross-infections following personal contact occurred wherever the disease broke out. For example, cases 1 and 4 were transferred from Gray's Inn Road to the private block at Liverpool Road and a nurse who attended case 4 became ill 6 days later. During the incubation period she had accompanied a surgical case from ward to operating theatre, remained in attendance during the operation, and escorted the case to bed in a different ward. The patient, the first

ward sister, the theatre sister, a medical officer, a medical student working in the theatre, and the second ward sister all became ill within 8 days. There was also a chance that the disease was spread through casual contact because several people incubating the infection whose usual base was Gray's Inn Road paid routine visits to Liverpool Road during the same week. More precise evidence pointed rather to close personal contact as an important factor in spreading the disease. For example, a first-year student nurse, working in one of the surgical wards mentioned in the previous paragraph, received a visit from her younger sister and her friend who had recently entered the Preliminary Training School at College Crescent. The three girls had tea together in the Nurses' Home and this, as far as is known, was the only occasion when members of the College Crescent community were exposed. The three girls contracted the disease within 8 days. A small explosive outbreak then followed in the closed community at College Crescent, providing an opportunity to observe the spread of infection in a select population.

SPREAD IN A SMALL 'CLOSED' COMMUNITY

At the time there were 27 student nurses under the age of 20, and 13 staff (between 25 and 50 years) including two men who were porters. The Training School is housed in a building which was once a small children's hospital and originally a large private house. Some student nurses are obliged to share bedrooms. Of the total population (40) only 8 contracted the disease, of whom 7 were student nurses. All the cases occurred over a 10-day period. The population was under close observation and suspect cases were admitted to hospital without delay. It seemed to be an ideal opportunity for spread among members of a highly susceptible age group. Only 25·8 % of the girls in that age group became clinical cases which were graded thus: severe 1, moderately severe 2, mild 5. Two of the mild cases were abortive, and in other circumstances would probably not have been admitted to hospital. Room-mates were sometimes, but not necessarily, at risk from one another. In this connexion some of the domestic staff at Gray's Inn Road were obliged to share bedrooms and room-mates were affected in only one instance.

Communal life

Many examples may be cited of presumable case-to-case spread among people in daily contact, whether this contact was related to work, feeding or recreation. There seemed to be no doubt that repeated close contact between two individuals was a greater risk than occasional contact, and this is illustrated in Fig. 5 and Table 7.

AETIOLOGY

The investigations carried out were (1) pathological, and (2) electro-diagnostic. An inquiry was made into the incidence of virus diseases among the nurses attending Sick Bay in the first 6 months of 1955.

Pathological investigations

Bacterial and virus isolation material was obtained at various stages of infection and included throat gargles, throat, nose and post-nasal swabbings, blood cultures, faeces and rectal swabs. The investigations included inoculation of fertile eggs,

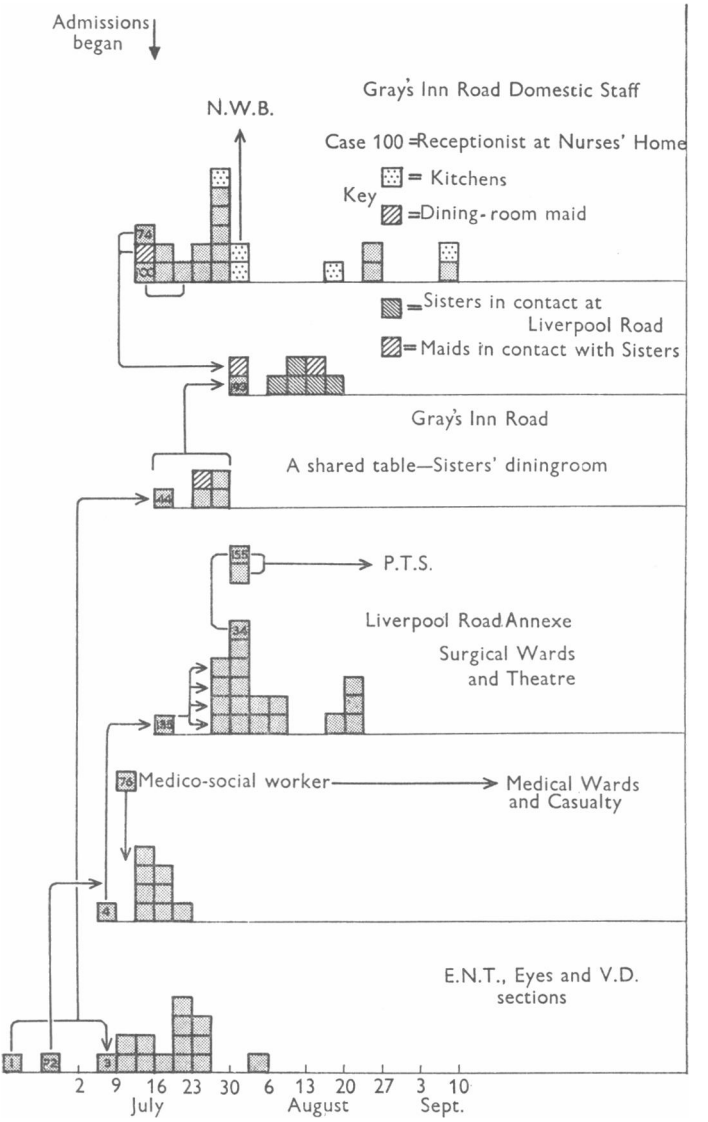

Fig. 5. Cases in small working and social groups: case-to-case infection.

suckling mice, adult mice, rats, ferrets, guinea-pigs, hamsters and rhesus monkeys. Tissue cultures of HeLa cells, monkey kidney, human embryo, human infant kidney, and human amnion were also inoculated. Experiments are continuing with additional animal species, tissue cultures and selective bacterial cultures. At

present a virus has not been isolated, and no known infectious agent has been found in the bacterial flora.

Serological tests were made relating to a variety of viral, protozoal and bacterial infections, namely influenza, psittacosis, APC syndrome, herpes simplex, Q fever, encephalomyocarditis, toxoplasmosis and leptospiral infection, all with negative results. Paired sera, acute phase and second phase were obtained from about a third of the cases and all samples of sera have been preserved for further investigation.

The Paul Bunnell test was performed on 121 cases, of which 94 showed a heterophile antibody titre of 1/40 or higher. After absorption with guinea-pig kidney and ox cells, 33 had Forssman type antibody, 57 cases had serum-sickness type antibody, 4 cases had infectious mononucleosis type antibody, and in the remainder, all of low titre, the pattern was blurred. The Wasserman reaction was carried out on 60 sera; there were no false positive results.

Blood picture. More than 50% of the cases showed morphological changes affecting about a quarter of the lymphocytes, without significant quantitative changes in the total white cells. The abnormalities, usually noted in the first week, were of the type previously associated with certain viral infections, though not with diseases caused by neurotropic viruses. The number of large lymphocytes was increased, the adult forms showing vacuolation of the cytoplasm. Immature forms of the lymphocytic series and the plasma-cell series were present. In the majority of cases there were no gross changes of the kind usually seen in sporadic cases of infectious mononucleosis.

Biochemical tests were made on sera of 119 patients. Three patients with enlarged tender livers showed mild abnormalities in colloidal gold and thymol reactions. In one case, complicated by jaundice at the height of the disease, serum bilirubin, thymol turbidity and alkaline phosphatase were abnormally increased. Excess urobilinogen was found in two of the patients who had other evidence of hepatitis.

The cerebro-spinal fluid was fully examined in 8 cases and showed no significant abnormality.

Histopathological material. No specific changes were observed in the very limited material available for histological examination. This consisted of two appendices showing mild hyperplasia of the lymphoid tissue, a small lymph node, excised 2 weeks after the onset of the disease, which showed well-marked reactive hyperplasia of non-specific type. Post-mortem tissue was examined from two further cases, both of whom had died from other causes several months after an attack of the epidemic disease. One of these fatal cases showed an ovarian carcinoma with multiple metastases and a terminal clostridial peritonitis and septicaemia. Microscopic examination of the brain, spinal cord and peripheral nerves showed no abnormality except for that attributable to either the septicaemia or carcinomatosis.

The second fatality, due to acute carbrital poisoning, occurred in a woman, aged 32, who had the epidemic disease 7 months before death and who had had definite clinical evidence of organic disease of the central nervous system for the last 7 months of her life. Post-mortem examination revealed small, circumscribed, grey or yellowish plaques in the white matter of the cerebral hemispheres, mainly

para-ventricular in distribution, in the brain stem and in the spinal cord, particularly in the cervical segment. Microscopic examination showed multiple, small, well, or fairly well, demarcated areas of demyelination with associated microglial and astrocytic proliferation and a variable degree of gliosis. There was no evidence of primary neuronal damage and no viral cell-inclusions were seen. Occasional cellular foci composed of lymphocytes and cerebral histiocytes, mainly perivascular in distribution, were present in the leptomeninges overlying the brain, but this was not a marked feature except in one section taken from the hypothalamus which showed intense perivascular cuffing.

This distribution and character of the lesions in the central nervous system, with the exception of the changes in the hypothalamus, were typical of disseminated sclerosis, and a histological diagnosis of disseminated sclerosis in a fairly early phase was made. The lesion in the hypothalamus in this case may represent the effects of a super-added viral encephalitis, but such an explanation is only conjectural and it is more probable that the intense perivascular cuffing represents an unusual, but not unknown, reaction associated with disseminated sclerosis.

Electrodiagnostic investigations

The nature of the muscular dysfunction was investigated by electromyographical methods. Richardson (1956), who studied 28 cases, has described the findings in 26 as typical of the so-called myelopathic lesion (Bauwens, 1955), namely, involvement of the motor unit at and above the level of the cord, with the additional feature of an unusual grouping of the motor units.

Sporadic infection of winter and spring of 1955

Respiratory infections. In the first 4 months of 1955, the Nurses' Sick Bay attendances were normal for the season. In April there were several cases of influenzal illness, of which two had Influenza A antibody. The monthly report for May noted an unusual number of sore throats for the time of year (11). The June report noted that the number of sore throats had decreased (5). *Streptococcus pyogenes* was isolated from two cases, one being clinically unresponsive to penicillin, but otherwise the bacteriological findings were negative.

Glandular fever. Between 1 March and 1 July there were four cases of mild sore throat with lymphadenopathy in which the clinical findings were consistent with a diagnosis of glandular fever (infectious mononucleosis). One only had heterophile antibody of the infectious mononucleosis type, accompanied by gross changes in the blood picture. Two showed qualitative changes in the mononuclear series of white cells consistent with those found in the epidemic disease.

Viscerotropic viral infections. A case admitted on 1 May had mild sore throat and jaundice. Clinical and chemico-pathological findings were consistent with the diagnosis of *infective hepatitis.* The Paul Bunnell test was not done. A case admitted on 9 April, with mild sore throat, lymphadenopathy, and rash, was tentatively diagnosed as rubella. Four cases did not allow of any diagnosis other than 'ill-defined virus disease'. Of all the cases noted here, there were 16 which

showed some, but not all, of the features of the epidemic disease as it appeared in July. None of the 16 had objective signs of neurological disorder. Four, however, were admitted in July when they were regarded as cases of the epidemic disease, i.e. new infections. It was not then appreciated that relapse and recrudescence were features of the illness, and had the first episodes occurred during the epidemic period, it is probable that they would have been regarded as mild cases with subsequent relapses varying in severity.

During the epidemic 4 cases were separately admitted in which the diagnosis of the current disease was not in question until the laboratory returned reports of positive Paul Bunnell tests. One such case had features of special interest.

A woman house officer who had experienced a mild attack of the epidemic disease in July was re-admitted in December as a case of severe relapse. The first attack in which there was typical transitory neurological disorder was graded as mild. After convalescence she returned to duty as a surgical house officer. On re-admission she displayed marked lympho-reticular involvement consistent with a diagnosis of infectious mononucleosis. The Paul Bunnell test, negative in July, was positive in December, and the blood changes were consistent with the diagnosis. Six days after her own re-admission her fiancé was admitted with a diagnosis of acute encephalomyelitis of the Royal Free Epidemic type. The engagement was recent, the young man worked elsewhere and was not otherwise connected with the hospital, where no new cases had occurred for some weeks, though there had been several suspects.

DISCUSSION

An idea of the epidemic syndrome as it varied between more than 300 cases is conveyed in the designation lympho-reticular encephalomyelopathy. The diversity of neurological disturbance gave rise to differing views of its pathology, but opinion was united in believing the disease to be infective in origin. This notion has not been displaced by the present failure to isolate the infectious agent, for the reason that the course of the illness is wholly consistent with changing phases of a host-parasite relationship which are reflected in the clinical picture. First, during the period of invasion, the parasite left traces of its passing in the pharynx and the regional lymphatic filter. Secondly, until the sudden onset of neurological disorder after several days, the disease was often silent, except in those who displayed tenderness of muscles, glands, liver, or spleen. This interval allowed time for an organism to disseminate, to pass the reticulo-endothelial defence barrier with greater or lesser ease in different hosts, and to multiply in the susceptible tissue before the pathogenic effect became clinically observable in the central nervous system. Thirdly, the morphological changes in mature lymphocytes and altered ratio of immature to mature mononuclear cells in the blood was additional evidence of activity in the antibody-forming cells of the host (Fagroeus, 1948; Bjørneboe & Gormsen, 1943). The presence of vacuoles in the cytoplasm of adult lymphocytes, which normally act as transporters of antibody (Burnet & Fenner, 1948; Marshall, 1953), and the corresponding increase of plasma cells and large lymphocytes suggests that both the antibody-synthesizers and transporters required replacement. This cellular reaction has been described in both bacterial and viral diseases, and has also been associated with allergic diseases (Litwins & Leibowitz, 1951). It is clear that it is evoked by a heterogeneous group of parasites and antigens.

In the Royal Free cases, changes in the blood picture were not necessarily correlated with clinical severity of neurological disturbance; the grosser cell changes, on the contrary, were seen in certain cases with marked lympho-reticular involvement, which included, with one exception, those with a previous history of infectious mononucleosis and infective hepatitis, and two or three cases with positive Paul Bunnell reactions. In many infections there is no evidence that the defence system of the host is less effective when the mechanism is silent, and it is therefore of some interest that in 14 of 20 cases silence was correlated with clinical severity. In other cases, not necessarily neurological, the reaction was reminiscent of the systemic protest associated with hypersensitivity, and the blood contained heterophile antibody of the serum sickness type. The titres were low, however, and not of the order reported either in serum sickness or pregnancy. The syndrome of infectious mononucleosis may be a manifestation of hypersensitivity excited by reinfection, after previous exposure to mild non-immunizing infections. There is no evidence that the particular type of heterophile antibody found in some, but not all cases with the syndrome, is specific in relation to a causal organism which has not been identified. Burnet (1955) suggested that the syndrome of infectious mononucleosis was a host reaction to a group of related viruses. It is possible that the heterophile antibody is produced by some, but not all, hosts in response to a particular form of antigenic stimulus, provided by any one member of a group of related organisms. It seems unjustifiable, in our present state of ignorance regarding the aetiology of either disease, to exclude three patients with positive Paul Bunnell tests as cases of infectious mononucleosis, when these were accepted on clinical grounds as cases of the epidemic disease. This finding, while throwing no light on the aetiology of the encephalomyelitis, may possibly contribute to knowledge of the aetiology of infectious mononucleosis.

In the hospital environment the disease appeared to be highly infectious and readily communicable. To a large extent these attributes were lost in the average home environment, though when home infections occurred they were not necessarily attenuated. The hospital environment offered many opportunities for a parasite to enter susceptible hosts in rapid succession, and if the causal organism had only a strictly limited term of viability outside the host it was always at a disadvantage in small heterogeneous communities.

The epidemic invited comparison with those simulating poliomyelitis which have occurred during the last decade in Iceland (Sigurdsson, Sigurjonsson, Sigurdsson, Thorkelsson & Gudmundsson, 1950), New York (White & Burtch, 1954), Adelaide (Pellew, 1951), Middlesex Hospital, London (Acheson, 1954), Coventry (Macrae & Galpine, 1954) and Durban (Hill, 1955). In Iceland, New York and Adelaide the diseases were observed in the general population, but no large institutional outbreak has been reported except that at the Addington Hospital, Durban. The diagnosis was clinical, and in no instance was the causal organism isolated. There was no evidence of transmission by blood-sucking insects as in the arthropod-borne viral encephalitides typified by St Louis encephalitis. A parallel variability of neurological disorder was also observed in von Economo's disease (encephalitis lethargica) in which fatal fulminating cases were distinguished

Table 9. *Epidemiological-clinical features of some types of encephalomyelitis in which virus was not isolated*

Royal Free Hospital 1955	Iceland 1948–9, New York 1950, Adelaide 1949–51, Durban 1955	von Economo's disease 1916–26 (encephalitis lethargica)
Summer–autumn	Autumn–winter	Winter–spring
All ages, mainly under 30	15–19 Iceland, New York; 5–9 Adelaide, student nurses Durban	All ages, mainly under 40
A series of explosive outbreaks in associated hospitals; limited spread in associated households	Multiple cases in households (Iceland); hospital outbreak (Durban); widespread (New York and Adelaide)	Widespread distribution but mode of spread unknown
Presumably spread by personal contact	Presumably spread by personal contact (Iceland)	—
No case fatalities	No case fatalities	Fatal fulminating cases
Variable syndrome. A group of cases resembled poliomyelitis. Disease marked by lympho-reticular involvement and relapsing myalgia	Variable syndrome; all described as simulating poliomyelitis. All marked by recurrence of signs and symptoms	Variable syndrome; six or more clinical types including hypersomnolent, hyperkinetic, ataxic poliomyelitic and psychotic. Disease marked by post-encephalitic sequaelae
Changes in circulating lymphocytes of more than half the cases	Haematological findings unremarkable	—
No changes in C.S.F. (8 only)	C.S.F. changes noted, often slight and not identical in different epidemics	C.S.F. changes recorded, but examination often negative

as a clinical type, a measure of the virulence of the infectious agents. The virus, which disappeared after the pandemic 1916–26, having affected people of all ages, was not isolated, and nothing is known regarding its host range and survival. Clinically the Royal Free disease resembled both Iceland disease and some clinical types of von Economo's disease in its milder forms (see Table 9). Sigurdsson *et al.* (1950) pointed out that during the Iceland epidemic the illness so nearly simulated poliomyelitis that the new disease was differentiated by consideration of the cumulative evidence and failure to isolate poliomyelitis virus. During the Royal Free epidemic a group of cases simulating poliomyelitis was distinguished as a clinical type but in general there was so little similarity that the anxiety of the lay population on this score was not at first appreciated.

The pattern of the previous virus experience will affect both the ratio of clinical to abortive cases and the incidence of hypersensitivity phenomena, thus changing the clinical aspect of the same infectious disease observed in different places. The lympho-reticular reaction which was a feature of the Royal Free epidemic may be an expression of this pattern. The same factors which influence clinical manifestations, namely the assortment of partially immune hosts, will also affect epidemiological aspects, such as differences of disease incidence in households, even where the disease is caused by the same pathogenic species. It is therefore possible that the Royal Free disease is an example of benign myalgic encephalomyelitis recently

postulated as a nosological entity (*Lancet*, 1956). On the other hand, it is possible that diseases caused by two different pathogenic species may simulate each other in different populations.

SUMMARY

An outbreak of encephalomyelitis of unknown aetiology occurred in the Royal Free Hospital Teaching Group in 1955. The disease which affected about 9 % of the population was probably a viral infection spread by personal contact. People of all ages were attacked but those under 30 were most susceptible. Institutional life was an important factor in determining the case incidence which was highest among nurses, orderlies and resident domestic staff. The clinical picture was one of encephalomyelopathy, with lympho-reticular reaction and relapsing myalgia.

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